# NSAIDs & Coxibs

For the purposes of clarity in this article NSAID refers to a "conventional NSAID" such as diclofenac, naproxen, ibuprofen, piroxicam etc. The term coxib refers to a COX-2 selective inhibitor such as rofecoxib, celecoxib, etoricoxib, lumiracoxib, meloxicam etc.

***Cardiovascular risk associated with NSAIDs and coxibs***

Evidence that rofecoxib (Vioxx) increases the risk of myocardial infarction has led to intensive research to assess the risks associated with other coxibs and NSAIDs. This research has confirmed that some of these drugs can also increase the risk of cardiovascular events but the mechanisms and clinical significance are still under intense debate.

**Key research findings**

- All NSAIDs and coxibs appear to have the capacity to cause oedema, hypertension and heart failure.
- Diclofenac, indomethacin, celecoxib, meloxicam and possibly ibuprofen are associated with an increased risk of cardiac events.
- Coxibs in general appear to increase cardiovascular risk but there are no data to indicate which drug is safest.
- Naproxen does not appear to increase cardiovascular risk suggesting that it is the safest NSAID with respect to cardiovascular toxicity. There is no evidence that naproxen is actually cardioprotective.
- It is not known if aspirin protects against increased cardiovascular risk caused by NSAIDs or coxibs. The evidence to support the claim that ibuprofen attenuates the cardioprotective effects of aspirin is still inconclusive.

**Background**

Coxibs were introduced with the promise of reduced gastrointestinal effects but with similar or superior effectiveness than existing NSAIDs. However the VIGOR and APPROVE trials and the subsequent withdrawal of rofecoxib due to an association with increased cardiovascular mortality cast doubt on the cardiovascular safety of the other coxibs. It followed logically that the cardiovascular safety of NSAIDs in general should be explored as it had long been known that all these drugs cause fluid retention and can increase blood pressure.

**Latest studies**

**Two recent studies have affirmed concerns about increased cardiovascular risk associated with NSAIDs and coxibs. For celecoxib the risk appears to increase with dose. Of the NSAIDs, diclofenac is associated with the greatest increase in risk and naproxen appears to be neutral but not cardioprotective.**

Further information on the cardiotoxicity of NSAIDs and coxibs has come from two recent studies. Kearney et al. performed a meta-analysis on 138 randomised controlled trials which included information on serious vascular events (MI, stroke or vascular death). Acute MI risk was increased by rofecoxib and celecoxib compared with placebo. The risk associated with celecoxib was greater at higher doses (400 mg per day and above). Combined vascular events (mainly MI) were increased by diclofenac compared with placebo and approached statistical significance with ibuprofen vs placebo. An increase in risk was not apparent with naproxen (Kearney, 2006).

A systematic review of observational studies (McGettigan, 2006) showed that cardiovascular risk (mainly MI) was increased by a number of drugs; a summary of the results is presented in Table 1. Rofecoxib increased cardiovascular risk in a dose related fashion which was evident early in treatment. For celecoxib no increased risk was found at doses of approximately 200 mg per day but the authors did not exclude the possibility of increased risk at higher doses. This possibility is supported by the results of an earlier study which indicate that cardiotoxicity with celecoxib is probably dose related (Solomon, 2006).

Diclofenac increased the risk of cardiovascular event at commonly used doses. A slightly increased risk was found with meloxicam (Mobic) but results with ibuprofen were inconclusive. Naproxen appeared to have a neutral risk but was not found to be cardioprotective as previously suggested.

| Table 1. Relative risk for cardiovascular event | |
|---|---|
| **Drug** | **Summary Relative Risk for Cardiovascular Event (95% CI)** |
| Naproxen | 0.97 (0.87 - 1.07) |
| Celecoxib | 1.06 (0.91 - 1.23) |
| Piroxicam | 1.06 (0.70 - 1.59) |
| Ibuprofen | 1.07 (0.97 - 1.18) |
| Meloxicam | 1.25 (1.00 - 1.55) |
| Indomethacin | 1.30 (1.07 - 1.60) |
| Rofecoxib ≤ 25 mg | 1.33 (1.00 - 1.79) |
| Diclofenac | 1.40 (1.16 - 1.70) |
| Rofecoxib > 25 mg | 2.19 (1.64 - 2.91) |
| Source McGettigan and Henry, 2006 | |

**Low dose aspirin and coxibs or NSAIDs**

There is no reliable evidence that combining a coxib with aspirin causes fewer ulcer complications than a conventional NSAID plus aspirin. In trials, sub-group analyses in people taking aspirin have found no statistically significant differences in ulcer complication rates between coxibs and NSAIDs (NPS, 2005). Furthermore, if low dose aspirin is added to a coxib the result is similar gastrotoxicity rates to NSAID alone. The effect of combining low dose aspirin with ibuprofen is still controversial. It has been suggested that ibuprofen actually reduces the antiplatelet effects of aspirin. The analysis by McGettigan and Henry found no evidence of this and until the situation becomes clearer there is no compelling evidence to switch patients who are stabilised on this combination. Aspirin will increase the risk of gastrotoxicity in all people taking a coxib or NSAID and gastroprotection should be considered in those at highest risk.

**Avoid coxibs and NSAIDs for people with heart failure**

A study which looked at the risk of hospital admission for heart failure in users of NSAIDs signals that certain patient groups are at high risk of NSAID-induced adverse effects (Huerta, 2006). In the cohort of people aged > 60 years, taking NSAID was associated with a 30% increase in the risk of hospital admission due to heart failure (RR 1.3; 1.1 - 1.6). The risk was much higher in people with pre-existing heart failure (RR 8.6; 5.34 - 13.84) and those taking two antihypertensive drugs (RR 3.76; 2.7 - 5.24). In addition a history of diabetes or renal failure also increased the risk of admission for heart failure. Two important points to note are that the risk of admission was slightly higher at the start of treatment and that although naproxen does not appear to increase the risk of cardiovascular events it was, with other NSAIDs, implicated in increasing the risk of admission for heart failure. The results of this study highlight the importance of assessing the risk of heart failure when considering the use of NSAID particularly in older persons. This study did not include people taking coxibs but there is no evidence that these drugs are safer than NSAIDs in this context.

**Relative safety of NSAIDs and coxibs**

Evidence is emerging that naproxen is neutral for cardiovascular risk but although naproxen has sustained antiplatelet effects this does not appear to confer cardioprotective. Of the commonly used NSAIDs; diclofenac and indomethacin are associated with the highest risk. The situation with coxibs is debateable. Rofecoxib carries the highest risk but has now been discontinued. Celecoxib may pose a low risk at doses of 200 mg per day or less but there is evidence that the risk increases at higher doses (Solomon, 2006). Etoricoxib (Arcoxia) is currently under scrutiny as the results of the recent MEDAL program demonstrated similar rates of cardiovascular events when compared with diclofenac. This in itself could be viewed as reassuring but the results are tempered by the fact that the comparator (diclofenac) is associated with relatively high cardiovascular risk. In addition there were higher rates of discontinuations due to hypertension or oedema related adverse events in the etoricoxib group compared with diclofencac (personal communication Merck, New Zealand, 29 August 2006).

Evidence about the cardiovascular safety of lumiracoxib (Prexige) is limited. The recent TARGET trial (Farkouh, 2004) consisted of two sub studies, each involving about 9000 people followed over one year. One study

compared lumiracoxib with naproxen and the other with ibuprofen with about 25% of all patients also taking low dose aspirin. The trial found no significant differences in the number of cardiovascular events (stroke, MI or cardiovascular death) between lumiracoxib and naproxen or ibuprofen. The results are inconclusive due to the trials low statistical power and its relatively short duration. In addition the wide confidence intervals (RR 1.46; 0.89 - 2.37 vs naproxen and 0.76; 0.41 - 1.4 vs ibuprofen) indicate that a clinically significant increase in cardiovascular risk compared with naproxen and ibuprofen cannot be ruled out (NPS, 2005).

**Current advice**

- All NSAIDs and coxibs should be used at the lowest effective doses for the shortest possible duration.
- Consider use of paracetamol as an alternative or as a "sparing" agent to reduce total daily intake of NSAID or coxib.
- Review patients' cardiovascular status and risk factors (and modify if possible) during treatment.
- Avoid NSAIDs and coxibs in patients with heart failure or in those at high risk of progression to heart failure (e.g. post MI).
- In patients with a low absolute risk of cardiovascular event choice of NSAID should mainly be guided by individual tolerance to gastrointestinal side effects.
- A coxib (e.g. celecoxib) plus aspirin has similar gastrotoxicity to a NSAID alone.

Regulatory authorities including Medsafe in New Zealand are currently reviewing the data and further advice is expected in the next 2 - 3 months. Current advice is that all NSAIDs and coxibs have the potential to increase the risk of cardiovascular events. The absolute risk increase is likely to be higher in those with pre-existing risk factors. For example, if a NSAID or coxib were to double the risk of cardiovascular events, the absolute risk for a person with a five year risk of cardiovascular events of 2.5% would increase to 5%, whereas for a person with a five year risk of 15%, it would increase to 30% (NPS, 2005).

***NSAIDs in the treatment of acute soft tissue injuries***

- In most cases the use of NSAIDs to treat acute soft tissue injuries is unnecessary. Paracetamol is as effective in relieving the pain associated with acute soft tissue injuries and is cheaper and safer than NSAIDs
- The anti-inflammatory effects of NSAIDs may be detrimental to tissue healing.
- RICE and paracetamol are recommended for acute strains and sprains associated with common sports injuries.
- NSAIDs are widely available without prescription, increasing the potential for inappropriate use and adverse effects.
- Soft tissue injury associated with definite inflammatory conditions such as bursitis or synovitis and nerve pressure due to soft tissue proliferation may respond to short term use of NSAIDS. Whenever possible long term use of NSAIDs should be avoided. (adapted from Paoloni, 2005)

NSAIDs such as ibuprofen, diclofenac and naproxen are widely sold, prescribed and promoted for soft tissue injuries associated with sporting activities. Coxibs (e.g. celecoxib) are also used but to a lesser extent. We are all aware that these drugs are not without significant gastrointestinal adverse effects and recent concerns over their cardiovascular safety have emphasised the importance of judicious and safe prescribing. Aside from the safety issue there is increasing evidence that anti-inflammatory effects of NSAIDs may be detrimental to tissue healing in acute soft tissue injury as inflammation assists in tissue repair (Braund, 2006).

Whilst, for most sports injuries, NSAIDs are only taken short term, some people may self medicate for long periods in chronic slow to heal injuries such as a sprained ankle. Whether use is short or long term unnecessary prescribing and OTC purchase of these drugs may be a significant cause of medicines related harm. Paracetamol is a cheaper and safer alternative to NSAIDs in relieving the pain of most soft tissue injuries (Paoloni, 2005).

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